US009636416B2

(12) **United States Patent**
Peters et al.

(10) **Patent No.: US 9,636,416 B2**
(45) **Date of Patent: *May 2, 2017**

(54) **IMMUNOGLOBULIN CHIMERIC MONOMER-DIMER HYBRIDS**

(71) Applicant: **Bioverativ Therapeutics Inc.**, Waltham, MA (US)

(72) Inventors: **Robert T. Peters**, Needham, MA (US); **Adam R. Mezo**, Waltham, MA (US); **Daniel S. Rivera**, Providence, RI (US); **Alan J. Bitoni**, Acton, MA (US); **Susan C. Low**, Pepperell, MA (US)

(73) Assignee: **Bioverativ Therapeutics Inc.**, Waltham, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/530,256**

(22) Filed: **Oct. 31, 2014**

(65) **Prior Publication Data**

US 2015/0139947 A1 May 21, 2015

Related U.S. Application Data

(60) Division of application No. 13/667,951, filed on Nov. 2, 2012, now Pat. No. 8,932,830, which is a division of application No. 12/952,551, filed on Nov. 23, 2010, now Pat. No. 8,329,182, which is a division of application No. 11/588,431, filed on Oct. 27, 2006, now Pat. No. 7,862,820, which is a continuation of application No. 10/841,250, filed on May 6, 2004, now Pat. No. 7,404,956.

(60) Provisional application No. 60/539,207, filed on Jan. 26, 2004, provisional application No. 60/487,964, filed on Jul. 17, 2003, provisional application No. 60/469,600, filed on May 6, 2003.

(51) **Int. Cl.**

C07K 14/475	(2006.01)
A61K 47/48	(2006.01)
C07K 14/505	(2006.01)
C07K 14/555	(2006.01)
C07K 14/56	(2006.01)
C07K 14/565	(2006.01)
C07K 14/745	(2006.01)
C07K 16/00	(2006.01)
C12N 9/64	(2006.01)
C12N 9/96	(2006.01)

(52) **U.S. Cl.**

CPC .. ***A61K 47/48369*** (2013.01); ***A61K 47/48215*** (2013.01); ***A61K 47/48415*** (2013.01); ***A61K 47/48423*** (2013.01); ***C07K 14/475*** (2013.01); ***C07K 14/505*** (2013.01); ***C07K 14/555*** (2013.01); ***C07K 14/56*** (2013.01); ***C07K 14/565*** (2013.01); ***C07K 14/745*** (2013.01); ***C07K 16/00*** (2013.01); ***C12N 9/644*** (2013.01); ***C12N 9/647*** (2013.01); ***C12N 9/6437*** (2013.01); ***C12N 9/96*** (2013.01); ***C12Y 304/21021*** (2013.01); ***C12Y 304/21022*** (2013.01); *C07K 2317/52* (2013.01); *C07K 2319/00* (2013.01); *C07K 2319/30* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,941,763	A	3/1976	Sarantakis	
4,456,591	A	6/1984	Thomas	
4,695,623	A	9/1987	Stabinsky	
4,784,950	A	11/1988	Hagen et al.	
4,831,119	A	5/1989	Nordfang et al.	
4,897,471	A	1/1990	Stabinsky	
5,077,204	A	12/1991	Brake et al.	
5,093,246	A	3/1992	Cech et al.	
5,116,753	A *	5/1992	Beattie	A61K 47/48238 435/34
5,116,964	A	5/1992	Capon et al.	
5,162,220	A	11/1992	Oshima et al.	
5,175,096	A	12/1992	Hoeoek et al.	
5,180,583	A	1/1993	Hedner	
5,189,015	A	2/1993	Hoeoek et al.	
5,234,830	A	8/1993	Oshima et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2045869 A1	12/1991
EP	0325262 A2	7/1989

(Continued)

OTHER PUBLICATIONS

Advisory Action mailed Jul. 12, 2007 for U.S. Appl. No. 10/841,250, filed May 6, 2004.

Advisory Action mailed Apr. 18, 2007 for U.S. Appl. No. 10/841,250, filed May 6, 2004.

Amendment/Req. Reconsideration-After Non-Final Office Action mailed May 21, 2007 for U.S. Appl. No. 11/029,003, filed Jan. 5, 2005.

Argos, P., "An Investigation of Oligopeptides Linking Domains in Protein Tertiary Structures and Possible Candidates for General Gene Fusion," Journal of Molecular Biology 211(4):943-958, Elsevier Ltd, New York, (1990).

Armour, K.L., et al., "Recombinant Human IgG Molecules Lacking Fcγ Receptor I Binding and Monocyte Triggering Activities," European Journal of Immunology 29(8):2613-2624, Wiley-VCH Verlag GmbH, Germany (1999).

(Continued)

Primary Examiner — Michelle S Horning

(74) *Attorney, Agent, or Firm* — Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

The invention relates to a chimeric monomer-dimer hybrid protein wherein the protein comprises a first and a second polypeptide chain, the first polypeptide chain comprising at least a portion of an immunoglobulin constant region and a biologically active molecule, and the second polypeptide chain comprising at least a portion of an immunoglobulin constant region without the biologically active molecule of the first chain. The invention also relates to methods of using and methods of making the chimeric monomer-dimer hybrid protein of the invention.

22 Claims, 27 Drawing Sheets